

ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, or an N-terminal fragment of at least 50 contiguous amino acid residues thereof, wherein said *hedgehog* polypeptide binds to a naturally occurring *patched* receptor, and wherein said amount of the *hedgehog* polypeptide is effective to promote one or more of growth, differentiation, and survival of said cells.

124. **(Amended)** A method for promoting survival of mammalian neuronal cells responsive to *hedgehog* induction, comprising treating the cells with an effective amount of a *hedgehog* polypeptide at least 80% identical to at least one sequence selected from SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, or an N-terminal fragment of at least 50 contiguous amino acid residues thereof, wherein said *hedgehog* polypeptide binds to a naturally occurring *patched* receptor, and wherein said amount of the *hedgehog* polypeptide is effective to increase the survival of the neuronal cells.

125. **(Amended)** A method for promoting growth of mammalian neuronal stem cells, comprising treating the cells with an amount of a *hedgehog* polypeptide at least 80% identical to at least one sequence selected from SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, or an N-terminal fragment of at least 50 contiguous amino acid residues thereof, wherein said *hedgehog* polypeptide binds to a naturally occurring *patched* receptor, and wherein the amount of the *hedgehog* polypeptide is effective to increase the rate of growth of the neuronal stem cells.

126. **(Amended)** The method of any one of claims 123, 124, or 125, wherein said *hedgehog* polypeptide is administered in combination with one or more other neurotrophic factors.

127. **(Reiterated)** The method of claim 126, wherein said other neurotrophic factor is selected from CNTF, BDNF, and NGF.

128. **(Reiterated)** The method of claim 123, wherein said neuronal cells are neural progenitor cells.

129. **(Reiterated)** The method of claim 123, wherein said neuronal cells differentiates into cells having a selected neural phenotype.
130. **(Reiterated)** The method of claim 123, wherein said neuronal cells are in the central nervous system or the peripheral nervous system.
131. **(Reiterated)** The method of claim 130, wherein said *hedgehog* treatment repairs central or peripheral nerve damage.
133. **(Amended)** The method of claim 123, wherein said *hedgehog* polypeptide comprises an amino acid sequence identical with an amino acid sequence designated in one of SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, or a fragment of at least 50 contiguous amino acid residues thereof.
134. **(Reiterated)** The method of any one of claims 123, 124, or 125, wherein said *hedgehog* polypeptide has an amino acid sequence which is encoded by a nucleic acid which hybridizes under highly stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence selected from SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6 and SEQ ID NO: 7.
135. **(Amended)** The method of claim 123, wherein said *hedgehog* polypeptide is encoded by a nucleic acid which is at least 98% identical with at least one of a nucleic acid sequence designated in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, or a fragment of at least 150 nucleotides thereof.
136. **(Amended)** The method of claim 123, wherein said *hedgehog* polypeptide is encoded by a nucleic acid which is at least 90% identical with at least one of a nucleic acid sequence designated in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, or a fragment of at least 150 nucleotides thereof.
137. **(Amended)** The method of claim 123, wherein said *hedgehog* polypeptide is encoded by a nucleic acid which is at least 95% identical with at least one of a nucleic acid sequence

designated in SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, or a fragment of at least 150 nucleotides thereof.

138. **(Amended)** The method of claim 123, wherein said polypeptide includes a *hedgehog* amino acid sequence at least 90 percent identical with a sequence selected from residues 104-189 of SEQ ID NO: 8, residues 102-187 of SEQ ID NO: 9, residues 31-116 of SEQ ID NO: 10, residues 102-187 of SEQ ID NO: 11, or residues 101-186 of SEQ ID NO: 12.

139. **(Reiterated)** The method of claim 123, wherein said polypeptide includes a *hedgehog* amino acid sequence at least 90 percent identical with a sequence selected from residues 27-189 of SEQ ID NO: 8, residues 22-187 of SEQ ID NO: 9, residues 1-116 of SEQ ID NO: 10, residues 25-187 of SEQ ID NO: 11, or residues 24-186 of SEQ ID NO: 12.

140. **(Amended)** The method of claim 123, wherein said polypeptide includes a *hedgehog* amino acid sequence at least 90 percent identical with an amino acid sequence selected from residues 27-425 of SEQ ID NO: 8, residues 22-396 of SEQ ID NO: 9, residues 1-336 of SEQ ID NO: 10, residues 25-437 of SEQ ID NO: 11, residues 24-418 of SEQ ID NO: 12, residues 24-475 of SEQ ID NO: 13, or residues 1-312 of SEQ ID NO: 14.

141. **(Reiterated)** The method of claim 123, wherein said polypeptide includes an amino acid sequence encoded by a naturally occurring vertebrate *hedgehog* gene.

142. **(Reiterated)** The method of claim 141, wherein said *hedgehog* gene is a mammalian *hedgehog* gene.

143. **(Reiterated)** The method of claim 142, wherein said *hedgehog* gene is a human *hedgehog* gene.

144. **(Amended)** The method of claim 123, wherein said polypeptide includes an amino acid sequence which is encoded by at least a portion of a *hedgehog* gene of vertebrate origin selected from nucleotides 64-567 of SEQ ID NO: 1, nucleotides 64-561 of SEQ ID NO: 2, nucleotides 1-

348 of SEQ ID NO: 3, nucleotides 73-561 of SEQ ID NO: 4, and nucleotides 70-558 of SEQ ID NO: 5.

145. **(Reiterated)** The method of claim 123, wherein said amino acid sequence is represented in the general formula SEQ ID NO: 41.

146. **(Reiterated)** The method of claim 123, wherein said polypeptide includes at least 150 amino acid residues of the N-terminal half of a *hedgehog* protein.

147. **(Reiterated)** The method of claim 123, wherein said polypeptide binds to a naturally occurring *patched* receptor.

148. **(Reiterated)** The method of claim 147, wherein said *patched* receptor is a patched receptor of a vertebrate organism.

149. **(Reiterated)** The method of claim 123, wherein said neuronal cells are selected from motor neurons, cholinergic neurons, dopaminergic neurons, serotonergic neurons and peptidergic neurons.

150. **(Reiterated)** The method of claim 123, wherein said *hedgehog* amino acid sequence is represented in the general formula SEQ ID NO: 40.

151. **(Reiterated)** The method of claim 123, wherein said polypeptide includes at least 50 amino acid residues of the N-terminal half of a *hedgehog* protein.

152. **(Reiterated)** The method of claim 123, wherein said polypeptide includes at least 100 amino acid residues of the N-terminal half of a *hedgehog* protein.

153. **(Amended)** A method for promoting one or more of growth, differentiation, and survival of neuronal cells, comprising contacting said cells with an amount of a *hedgehog* polypeptide encodable by a nucleic acid which hybridizes under stringent conditions, including a wash step of  $0.2 \times \text{SSC}$  at  $65^\circ\text{C}$ , to a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID

NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, or a fragment thereof of at least 150 nucleotides, wherein said *hedgehog* polypeptide binds to a naturally occurring *patched* receptor, and wherein said amount of a *hedgehog* polypeptide is effective to promote one or more of growth, differentiation, and survival of said cells.

154. **(Amended)** A method for promoting survival of mammalian neuronal cells responsive to *hedgehog* induction, comprising treating the cells with amount of a *hedgehog* polypeptide effective to promote the survival of neuronal cells, wherein said *hedgehog* polypeptide is encodable by a nucleic acid which hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, or a fragment thereof of at least 150 nucleotides, wherein said *hedgehog* polypeptide binds to a naturally occurring *patched* receptor.

155. **(Amended)** A method for promoting growth of mammalian neuronal stem cells, comprising treating the cells with an amount of a *hedgehog* polypeptide encoded by a nucleic acid which hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, or a fragment thereof of at least 150 nucleotides, wherein said *hedgehog* polypeptide binds to a naturally occurring *patched* receptor, and wherein said amount of a *hedgehog* polypeptide is effective to increase the rate of growth of the neuronal stem cells.

156. **(Amended)** The method of claim 125, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 90% identical to all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 7.

157. **(Amended)** The method of claim 125, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 95% identical to all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 7.

158. **(Amended)** The method of claim 125, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 98% identical to all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 7.

159. **(Amended)** The method of claim 124, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 90% identical to all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 7.

160. **(Amended)** The method of claim 124, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 95% identical to all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 7.

161. **(Amended)** The method of claim 124, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 98% identical to all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 7.

162. **(Reiterated)** The method of claim 123, wherein the N-terminal fragment is approximately 19 kD.

163. **(Reiterated)** The method of claim 124, wherein the N-terminal fragment is approximately 19 kD.

164. **(Reiterated)** The method of claim 125, wherein the N-terminal fragment is approximately 19 kD.

*The claims presented above incorporate changes as indicated by the marked-up versions below.*

123. (Amended) A method for promoting one or more of growth, differentiation, and survival of neuronal cells, comprising contacting said cells with an amount of a *hedgehog* polypeptide at least 80% identical to at least one a sequence selected from SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, ~~SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID No: 20, SEQ ID NO: 21~~ and or an N-terminal fragments fragment of at least 50 contiguous amino acid residues thereof, wherein said *hedgehog* polypeptide of the preceding sequences that bind binds to a naturally occurring *patched* receptor, and wherein said ~~the~~ amount of the *hedgehog* polypeptide is effective to promote one or more of growth, differentiation, and survival of said cells.

124. (Amended) A method for promoting survival of mammalian neuronal cells responsive to *hedgehog* induction, comprising treating the cells with an effective amount of a *hedgehog* polypeptide at least 80% identical to at least one a sequence selected from SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, ~~SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID No: 20, SEQ ID NO: 21~~ and or an N-terminal fragments of the preceding sequences that bind fragment of at least 50 contiguous amino acid residues thereof, wherein said *hedgehog* polypeptide binds to a naturally occurring *patched* receptor, and wherein said amount of the *hedgehog* polypeptide is effective to increase thereby increasing the survival rate of the neuronal cells.

125. (Amended) A method for promoting growth of mammalian neuronal stem cells, comprising treating the cells with an amount of a *hedgehog* polypeptide at least 80% identical to at least one a sequence selected from SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, ~~SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID No: 20, SEQ ID NO: 21~~ and or an N-terminal fragment of at least 50 contiguous amino acid residues thereof, wherein said *hedgehog* polypeptide binds fragments of the preceding sequences that bind to a naturally occurring *patched* receptor, and wherein the amount of the *hedgehog* polypeptide is effective to increase the rate of growth of the neuronal stem cells.

126. (Amended) The method of any one of claims 123, 124, or 125, wherein said *hedgehog* ~~protein~~ polypeptide is administered in combination with one or more other neurotrophic factors.

133. (Amended) The method of claim 123, wherein said *hedgehog* polypeptide comprises an amino acid sequence identical with ~~all or a portion of~~ an amino acid sequence designated in one of SEQ ID NO: 8, SEQ ID NO: 9, SEQ ID NO: 10, SEQ ID NO: 11, SEQ ID NO: 12, SEQ ID NO: 13, SEQ ID NO: 14, or a fragment of at least 50 contiguous amino acid residues thereof and SEQ ID NO: 34.

135. (Amended) The method of claim 123, wherein said *hedgehog* polypeptide is encoded by a nucleic acid which is at least 98% identical with ~~all or a portion of~~ at least one of a nucleic acid sequence designated in ~~one of~~ SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7, or a fragment of at least 150 nucleotides thereof.

136. (Amended) The method of claim 123, wherein said *hedgehog* polypeptide is encoded by a nucleic acid which is at least 90% identical with ~~all or a portion of~~ at least one of a nucleic acid sequence designated in ~~one of~~ SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7, or a fragment of at least 150 nucleotides thereof.

137. (Amended) The method of claim 123, wherein said *hedgehog* polypeptide is encoded by a nucleic acid which is at least 95% identical with ~~all or a portion of~~ at least one of a nucleic acid sequence designated in ~~one of~~ SEQ ID NO: 1, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, and SEQ ID NO: 7, or a fragment of at least 150 nucleotides thereof.

138. (Amended) The method of ~~any one of~~ claim 123, wherein said polypeptide includes a *hedgehog* amino acid sequence at least ~~80~~ 90 percent identical with a sequence selected from residues 104-189 of SEQ ID NO: 8, residues 102-187 of SEQ ID NO: 9, residues 31-116 of SEQ ID NO: 10, residues 102-187 of SEQ ID NO: 11, or residues 101-186 of SEQ ID NO: 12.

140. (Amended) The method of claim 123, wherein said polypeptide includes a *hedgehog* amino acid sequence at least 90 percent identical with an amino acid sequence selected from residues 27-425 of SEQ ID NO: 8, residues 22-396 of SEQ ID NO: 9, residues 1-336 of SEQ ID NO: 10, residues 25-437 of SEQ ID NO: 11, residues 24-418 of SEQ ID NO: 12, ~~or~~ residues 24-475 of SEQ ID NO: 13, or residues 1-312 of SEQ ID NO: 14.



144. (Amended) The method of claim 123, wherein said polypeptide includes an amino acid sequence which is encoded by at least a portion of a *hedgehog* gene of vertebrate origin selected from ~~residues~~ nucleotides 64-567 of SEQ ID NO: 1, ~~residues~~ nucleotides 64-561 of SEQ ID NO: 2, ~~residues~~ nucleotides 1-348 of SEQ ID NO: 3, ~~residues~~ nucleotides 73-561 of SEQ ID NO: 4, and ~~residues~~ nucleotides 70-558 of SEQ ID NO: 5.

153. (Amended) A method for promoting one or more of growth, differentiation, and survival of neuronal cells, comprising contacting said cells with an amount of a *hedgehog* polypeptide encodable by a nucleic acid which hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, ~~SEQ ID NO: 8, or SEQ ID No: 19~~, or a fragment thereof of at least 150 nucleotides, wherein said *hedgehog* polypeptide ~~that~~ binds to a naturally occurring *patched* receptor, and wherein said amount of a *hedgehog* polypeptide is effective to promote one or more of growth, differentiation, and survival of said cells.

154. (Amended) A method for promoting survival of mammalian neuronal cells responsive to *hedgehog* induction, comprising treating the cells with ~~an effective~~ amount of a *hedgehog* polypeptide effective to promote the survival of neuronal cells, wherein said *hedgehog* polypeptide is encodable by a nucleic acid which hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, ~~SEQ ID NO: 8, or SEQ ID No: 19~~, or a fragment thereof of at least 150 nucleotides, wherein said *hedgehog* polypeptide ~~that~~ binds to a naturally occurring *patched* receptor, ~~thereby increasing the rate of survival of the neuronal cells~~.

155. (Amended) A method for promoting growth of mammalian neuronal stem cells, comprising treating the cells with an amount of a *hedgehog* polypeptide encoded by a nucleic acid which hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C, to a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, ~~SEQ ID NO: 8, or SEQ ID No:~~

~~19,~~ or a fragment thereof of at least 150 nucleotides, wherein said *hedgehog* polypeptide that binds to a naturally occurring *patched* receptor, and wherein said amount of a *hedgehog* polypeptide is effective to increase the rate of growth of the neuronal stem cells.

156. (Amended) The method of claim 125, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 90% identical to all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 7, ~~SEQ ID NO: 8, or SEQ ID No: 19.~~

157. (Amended) The method of claim 125, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 95% identical to all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 7, ~~SEQ ID NO: 8, or SEQ ID No: 19.~~

158. (Amended) The method of claim 125, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 98% identical to all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 7, ~~SEQ ID NO: 8, or SEQ ID No: 19.~~

159. (Amended) The method of claim 124, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 90% identical to all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 7, ~~SEQ ID NO: 8, or SEQ ID No: 19.~~

160. (Amended) The method of claim 124, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 95% identical to all or a portion of a nucleic acid sequence designated in one of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, or SEQ ID NO: 7, ~~SEQ ID NO: 8, or SEQ ID No: 19.~~

161. (Amended) The method of claim 124, wherein said polypeptide sequence comprises a polypeptide encoded by a nucleic acid which is at least 98% identical to all or a portion of a